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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/300,425	04/28/1999	DARIO NERI	113000.301	4446

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/300,425	NERI ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-17,19-34,36-43 and 49-51* is/are pending in the application.

4a) Of the above claim(s) *14-17,19,25-27 and 49-51* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-24,28-34 and 36-43* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/24/05. / 8/15/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13, 18, 35, 44-48 have been canceled.
Claims 14-17, 19-34, 36-43, 49-51 are pending.
Claims 14-17, 19,25-27, 49-50 and 51 stand withdrawn as they are claims directed to a method or dependent upon a canceled claim.
Claims 20-24, 28-34, 36-43 are under consideration.
1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections/Rejections Withdrawn

1. All objections and rejections over canceled claims are moot.
2. The number of the drawings is no longer objected to in view of the prior amendment setting forth with designators such as 1A, and 1B etc.
1. Claim 36 rejected under 35 USC 112, second paragraph for not reciting a reference sequence is maintained in light of the fact that SEQ ID Nos 30 and 32 only contain 4 amino acids and 6 amino acids respectively, and the claims are directed to sequences that contain up to 54 and 50 amino acids respectively, is herein withdrawn in light of the fact that claim 36 no longer SEQ ID NO 30 and 32.
2. The disclosure objected to because it contains an embedded hyperlink and/or other form of browser-executable code has been obviated through removal of the hyperlink.

Continued Examination Under 37 CFR 1.114

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 27, 2005 has been entered.

Information Disclosure Statement

4. The information disclosure statement filed August 15, 2005 has been considered.

Response to Arguments/ Rejections Maintained

1. Applicant states that a new copy of Table I had been previously provided and an additional copy was resubmitted with Applicant's response.

2. It is the position of the examiner that the prior Table 1 did not have the required SEQ ID Nos inserted and the new copy of Table 1 also does not show the required SEQ ID Nos.

1. The objection to the Specification for informalities at page 14, lines 13-20, and Table 1, page 27 which requested Resubmission of this amendment in the form with the **SEQ ID Nos inserted** is herein still maintained.

2. The amendment of the instant Specification directing the insertion of SEQ ID Nos into the Specification at page 27 was not entered as the SEQ ID Nos. were considered to be too extensive to entered. The new page 27 for substitution into the instant Specification that contained the required SEQ ID Nos was not received. The Amendment file September 1, 2000, was only partially entered; page 2 of the amendment was not entered. The examiner requested a New Table for all amino acid sequences of 4 or more amino acids in length. Applicant's resubmission of a request for amendment was not entered for the same responses previously made of record. Rotating the table 90 degrees would provide more room for setting forth the SEQ ID Nos and data provided in table I.

3. ***Provisional Double Patenting Maintained***: The rejection of Claims 20 of this application that is in conflict with claims 12-13 of Application No. 10/321,558 is traversed on the grounds that copending claims 12-13 are not defined to be conjugates and therefore a line of demarcation has been maintained between the two applications.

4. It is the position of the examiner that copending Application 10/321,558 defines the claimed composition at paragraph [009] to be a "radionuclide linked to a suitable vehicle", the vehicle being an antibody as defined in Application 10/321, 558. Thus while the term "linked" is

to define the claimed radiolabeled antibody, and there term "conjugate" is not recited, a linked radionuclide/antibody composition is produced through linking the radionuclide to the antibody by conjugation. A clear line of demarcation has not been maintained; the provisional rejection is maintained for reasons of record and responses set forth herein.

5. ***Claim Rejections - 35 USC § 112 (New Matter) , Rejection Maintained:*** The rejection of claims 20-24, 28-34, 36-43 rejected under 35 U.S.C. 112, first paragraph (New Matter) , as failing to comply with the written description requirement is traversed on the grounds that:

a. The instant Specification "clearly supports the concept of affinities "sub" *i.*e. "less than" nanomolar ($1X10^{-9}$ M) ;

b. The Specification repeatedly refers to antibodies of "improved" affinities; and

c. The entire Specification is drawn to the concept of improving affinities and points to antibodies E1, E2, G4, H10 and L10 the affinities of which are modified and further improved.

6. It is the position of the examiner that upon consideration of Table 2, page 28, the examiner found the dissociation constants for antibodies A2, G4, E1 and H10 to **be above the nanomolar range** and the only antibody with **subnanomolar binding,** was antibody **L19.** Table 2, only provides a single antibody that evidences subnanomolar binding and 4 antibodies above this binding range. The rejection made of record was based upon the fact that the Specification does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed highly variable genus of antibodies that comprise any one or more mutations in any of the residues of any of the antibody's CDR regions and evidences any K_d less than 54 pM while the instant Specification

only discloses antibody L19 of 54 pM which is not less than 54 pM, but equal to 54 pM. The specific range of 50-54 pM does not evidence original descriptive support in the instant Specification, the only range disclosed is 27-54 pM which is no longer claimed.

Within the claimed scope are antibodies of 1,2,3,4,5,6,7,8,9,10, 20, 21 pM affinities, but none of these antibodies evidence original descriptive support in the instant Specification. What is now claimed is Not a method of producing improved binding affinity antibodies, but compositions of antibodies. No antibodies in the femtamole binding range are described, and femtamole binding is a range that is encompassed by the claimed range of "less than 54 pM".

With respect to the recitation of the phrase 1-3 mutations, at any location within any of the antibody's CDRs, it is the position of the examiner that only specific mutations are disclosed and original descriptive support for the claimed range would not be found in the instant Specification, wherein the mutations resulted in improved binding. Upon consideration of the guidance and disclosure provided by Table 2, the examiner only found guidance for production of antibodies with binding affinities that are Not improved relative to antibody L19. The rejection is maintained for reasons of record.

New Grounds of Objection/Rejection

Drawings

5. Color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

6. Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2). . Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The drawings are objected to because Figure 1 is described based upon colors, yellow, blue and gray, but all patents are published in black and white; the description of the drawing Figure 1A, will be unclear upon issue of the instant Application as a patent. Clarification is requested.

Claim Objections

7. Claims 28-32, 37-39 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 28-32 and 37-39 depend from claim 20 which is directed to a genus of antibody conjugates that have dissociation constants of LESS than 54 pM, while claims 28-32 and 37-39 require the claimed conjugates include antibodies that evidence a dissociation constant EQUAL to 54 pM, thus adding additional inventions to the claimed genus of independent claim 20. Therefore, claims 28-32 and 37-39 are not further limiting of claim 20 from which the directly or indirectly depend as they are broader in scope.

8. Claims 36 and 43 are objected to because of the following informalities: Claims 36 and 43 recite the newly added phrase "wherein said antibody comprises the following amino acid sequence" and the phrase "at least one mutant in one or more of its CDR regions". These two phrases do not set forth a combination of claim limitations that are internally consistent. How can the antibody comprise SEQ ID Nos 19, 20 and 21, but when SEQ ID Nos 19, 20 and 21 are mutated they are not SEQ ID Nos 19, 20 and 21. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. Claims 20-24, 28-34 and 36-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling antibodies that will bind to the ED-B domain of Fibronectin, does not reasonably provide enablement for the specific antibodies with binding affinities of 27 and 54 pM (see claim 28 and all claims that depend therefrom, and depend from claim 20 and claim 37, 39) and evidence mutations that are functionally defined (claims 20, 36 and 43 "improved") and bind with a binding affinity of less than 54 pM. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use novel strains with unobvious characteristics the invention commensurate in scope with these claims.

The claims are directed to a specific monoclonal antibodies produced by a genetically unique hybridoma cell lines, that need a perfected deposit. For each deposit made pursuant to the Budapest Treaty regulations, shall contain:

(1) The accession number for the deposit;

(2) The date of the deposit;

(3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and

(4) The name and address of the depository.

(e) Any amendment required by paragraphs (d)(1), (d)(2) or (d)(4) of this section must be filed before or with the payment of the issue fee (see § 1.312).

[Added, 54 FR 34882, Aug. 22, 1989, effective Jan. 1, 1990; paras. (b) and (c) revised and para. (e) added, 66 FR 21092, Apr. 27, 2001, effective May 29, 2001]

As well as a statement that removes restrictions to provide access to this hybridoma and expressed monoclonal antibody upon granting of a patent has not made, either in the instant Specification, nor in Applicant's Remarks. One of the critical conditions of Deposit is defined in 37 CFR 1.808 requires that the deposit of biological material be made under two conditions: (A) access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. 122, and (B) with one exception, that all restrictions imposed by the depositor on the availability to the public of the deposited biological material be irrevocably removed upon the granting of the patent. Upon making this statement, the rejection under 35 USC 112, first paragraph will be withdrawn. This rejection can be obviated through perfection of the Deposit and amendment of the claims to clearly set forth the Deposited strains.

Double Patenting

10. Claims 20-24, 28-34, 36-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4 of copending Application No. 10/204, 584 (PG-Pub cited on USPTO 1449). Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending applications have not been allowed as yet and claim 4 is directed to a species of invention encompassed by the instant claims that are conjugates that comprise an antibody that will bind to the ED-B

domain conjugated to a cytotoxic or biocidal effect which includes a molecule that will induce blood coagulation and blood vessel occlusion, that is radiolabeled.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

11. Claims 20-24, 28-34, 36-43 are rejected under 35 U.S.C. 102(a) as anticipated by in light of evidence provided by Vaughan et al (1996).

Neri et al disclose antibodies (see page 11, lines 5-7, and all paragraphs on this page) and antibody conjugates (see page 1, lines 24-28;) that comprise a toxin, photosensitive (page 15, lines 12-17,) or radionucleotide(see page 16, lines 1-12) moiety/label with improved binding characteristics (see page 11, lines 5-7, "6X 10^{-8} or less for ED-B FN) directed to the ED-B domain of fibronectin (see all claims), and claims antibodies (see page 7, lines 25-36) and mutant antibodies(page 10, paragraph 1) obtained by a process of panning (see page 6, paragraphs 2-3) to obtain mutant antibodies that evidence improved binding characteristics specific for the ED-B domain of fibronectin. Inherently the antibodies that evidence a dissociation constant of "6X 10^{-8} or less for ED-B FN anticipate the instantly claimed antibody conjugates as the ranges for the antibody dissociation constants over lap in light of evidence provided by Vaughan et al that subnanomolar affinities in matured antibodies were known in the art in 1996 .

12. Claims 20-24, 28-34, 36-43 are rejected under 35 U.S.C. 103(a) as obvious over Neri et al (WO97/45544) in view of Vaughan et al (1996).

See discussion of Neri et al above. Neri et al teach, show, suggest, and provide guidance for the attainment of conjugate antibodies with improved binding for the ED-B domain of fibronectin, and suggest the attainment of antibodies in the subnanomolar range (6X 10^{-8} or less for ED-B FN) but differ from the instantly claimed invention by failing to show the methods taught to isolate an antibody formulated into a conjugate with subnanomolar range binding affinities.

Vaughn et al teach human antibodies with sub-nanomolar affinities isolated from a large phage library in an analogous art for the purpose of obtaining high affinity human antibodies directed against "any given antigen" by a rapid method (abstract second line) that results in a "stable, and reliable source of specific, high affinity human monoclonal antibodies".

It would have been obvious to the person to the person of ordinary skill in the art at the time the invention was made to follow the guidance, suggestions and teachings of Neri et al in order to obtain antibodies that evidence ED-B antigen binding characteristics in the subnanomolar range as described by Vaughn et al because both Vaughn et al and Neri et al are directed to that attainment of antibodies with improved binding specificities and affinities directed against a specific antigen, and Vaughn et al shows that antibodies with sub-nanomolar affinities are readily obtainable, as stable, and are obtained from a reliable source of specific high affinity human monoclonal antibodies (see Vaughn et al, abstract)

The person of ordinary skill in the art would have been motivated by the reasonable expectation of success, because Neri et al teach an "affinity maturation" process for obtaining antibodies with improved properties relative to the parent clones (see page 6, paragraphs 2-3) and Neri et al suggests the attainment of antibodies in the subnanomolar range for the purpose of

detecting the presence of ED-B in neovasculare structures associated with tumors and to also administer the matured antibodies with improved antibody binding to patients for tumor therapy see page 1, paragraph 1-2) and Vaughan et al showed that the process is readily applicable to "any given antigen" and results in antibodies with subnanomolar affinities for the desired antigen, and in the case of Neri et al, that antigen would be a tumor associated antigen, specifically ED-B domain of fibronectin.

In the absence of a showing of unexpected results, Neri et al in view of Vaughn et al obviate the instantly claimed invention as now claimed.

Conclusion

7. This is a non-final action.

8. Epstein, AL et al is cited to show a monoclonal antibody designated TV-1 that is specific to an antigen expressed in tumor vessels.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vgp
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